HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

14 December 2011

PROLIA 60 mg, solution for injection in a pre-filled syringe
Pack of 1 pre-filled syringe presented in blistered packaging - CIP code: 492 855 5
Pack of 1 pre-filled syringe not presented in blistered packaging - CIP code: 492 856 1
Pack of 1 pre-filled syringe with a needle guard presented in blistered packaging - CIP code: 492 857 8

PROLIA 60 mg, solution for injection
Pack of 1 vial (glass) - CIP code: 492 858 4

Applicant: AMGEN SAS

denosumab
ATC code : M05BX04

List I

Date of Marketing Authorisation: 28 May 2010 (centralised procedure, co-rapporteurs: Spain and The Netherlands)

Reason for request: Inclusion on the list of medicines reimbursed by National Health Insurance and approved for hospital use.

AMGEN have applied for PROLIA to be listed only for the indication "postmenopausal osteoporosis" and in a population restricted to female patients satisfying two of the following three criteria: age ≥ 70 years, T-score ≤ -3 or at least one previous fracture or having a contraindication to, poor tolerance of or failure of treatment for postmenopausal osteoporosis.
They have not applied for listing in the indication "Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures". However, for a first listing, the Transparency Committee has to give its opinion on all the indications in the Marketing Authorisation (article R. 163-18 of the Social Security Code).

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

denosumab

1.2. Background

PROLIA (denosumab) is the first biological agent to be made available for the treatment of postmenopausal osteoporosis and bone loss associated with hormone ablation in men with prostate cancer.

Denosumab is a human IgG2 monoclonal antibody with affinity and specificity for human RANK ligand (RANKL), inhibiting osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone.

1.3. Therapeutic indications

"Treatment of postmenopausal osteoporosis in women at increased risk of fractures. PROLIA significantly reduces the risk of vertebral, non vertebral and hip fractures.

Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, PROLIA significantly reduces the risk of vertebral fractures."

1.4. Dosage

"The recommended dose of Prolia is 60 mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm.
Patients must be adequately supplemented with calcium and vitamin D.

Renal impairment
No dose adjustment is required in patients with renal impairment.

Hepatic impairment
The safety and efficacy of denosumab have not been studied in patients with hepatic impairment.

Elderly patients (≥ 65)
No dose adjustment is required in elderly patients.

Paediatric population
PROLIA is not recommended in paediatric patients (age < 18) as the safety and efficacy of PROLIA in these patients have not been established. Inhibition of RANK/RANK ligand (RANKL) in animal studies has been coupled to inhibition of bone growth and lack of tooth eruption.

Method of administration
Administration should be performed by an individual who has been adequately trained in injection techniques. For subcutaneous use."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

M	: musculo-skeletal system
M05	: drugs for treatment of bone diseases
M05B	: drugs affecting bone structure and mineralization
M05BX	: other drugs affecting bone structure and mineralization
M05BAX04	: denosumab

2.2. Medicines in the same therapeutic category

There are no other medicines in the same category (monoclonal antibodies) with the same indications.

2.3. Medicines with a similar therapeutic aim

2.3.1 Postmenopausal osteoporosis

The relevant comparators are medicines that have demonstrated their efficacy in the prevention of vertebral and peripheral fractures, including femoral neck fractures:

- the following bisphosphonates:
  - ACLASTA 5 mg (zoledronic acid), IV infusion (once a year),
  - ACTONEL (risedronic acid) 5 mg tablet (daily), 35 mg (weekly), 75 mg (two consecutive days a month), ACTONELCOMBI (risedronate 35 mg + calcium 1000 mg + vitamin D 880 IU) tablets (weekly),
  - FOSAMAX (alendronic acid) 10 mg tablets (daily), 70 mg (weekly) and other medicinal products containing alendronic acid 10 mg and 70 mg FOSAVANCE and ADROVANCE (alendronate or combination of alendronate + vitamin D) tablets weekly.

The actual benefit of these medicinal products is substantial.

- PROTELOS (strontium ranelate) granules for oral suspension (daily), ATC code M05BX03 similar to that of denosumab, drugs affecting bone structure and mineralisation.
  In May 2011, in view of concerns about the risk of onset of DRESS and venous thromboembolism, the actual benefit of PROTELOS was classed as moderate in a population restricted to:
  - patients with a contraindication to or adverse effects with bisphosphonates,
  - patients with no risk factors for venous thromboembolism, including a history of venous thromboembolism, age over 80 years, prolonged immobility, etc..

As a reminder, the Committee states that other medicines are indicated in postmenopausal osteoporosis but have only been shown to be effective in preventing vertebral, but not femoral neck, fractures.

The following bisphosphonates:

- BONVIVA 3 mg solution for injection in pre-filled syringe (ibandronic acid), every three months and BONVIVA 150 mg tablets (once a month)
- DIDRONEL 400 mg tablets and generic versions (etidronic acid), daily

The actual benefit of these medicines has been classed as insufficient since December 2010.

- SERM (selective oestrogen receptor modulators):
  - EVISTA and OPTRUMA (raloxifene), tablets (daily) efficacy against vertebral fractures only, actual benefit substantial;
  - COMBRIZA (bazedoxifene), tablets (daily) efficacy against vertebral fractures only, currently being evaluated.
- parathyroid hormone derivative:

- o FORSTEO (teriparatide), subcutaneous injection daily, actual benefit substantial, reimbursed for patients with severe osteoporosis (at least two vertebral fractures), efficacy demonstrated against peripheral but not hip fractures;
- o PREOTACT (PTH 1-84) not marketed.

Calcium and vitamin D are generally used as adjuvant therapy.

2.3.2. Bone loss in prostate cancer

No other medicines have this specific indication.
However, some bisphosphonates (alendronic acid, risedronic acid, zoledronic acid) and teriparatide are indicated in osteoporosis in men.
However, the efficacy of these medicines against fractures has not been demonstrated in men. Other intravenous bisphosphonates are used to prevent bone complications; their actual indications are given in the table below:

DRUGS FOR INJECTION		
INN	**Proprietary medicinal product**	**Indication**
clodronic acid	CLASTOBAN 300 mg/5 mL ampoule	Initial treatment of severe tumour-induced hypercalcaemia. Treatment should be combined with optimum rehydration. Treatment should be given only for the time needed to restore normal blood calcium concentration
ibandronic acid	BONDRONAT 6 mg concentrate for solution for infusion (2 mg approved for use by hospitals only)	"Prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases. Treatment of tumour-induced hypercalcaemia with or without metastases." (indication not reimbursable)
pamidronic acid	AREDIA powder and solvent for solution for infusion and essentially similar medicines	Initial treatment of severe tumour-induced hypercalcaemia - Treatment of stage III myeloma with at least one bone lesion; - Palliative treatment of tumour-induced osteolysis with or without hypercalcaemia in addition to specific treatment of the tumour; - Treatment of Paget's disease of bone.
zoledronic acid	ZOMETA 4 mg/ 5 mL, concentrate for solution for infusion	Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in adult patients with advanced malignancies involving bone. Treatment of tumour-induced hypercalcaemia (TIH)

The actual benefit of these medicinal products is substantial.

3 ANALYSIS OF AVAILABLE DATA

3.1. Treatment of postmenopausal osteoporosis

The clinical development of denosumab (started in 2001) in postmenopausal osteoporosis is based on a pivotal placebo-controlled study of its efficacy in preventing fractures, the FREEDOM study[1]- 20030216 and three studies of its efficacy on an intermediate criterion, bone mineral density (BMD) compared with alendronate. The FREEDOM trial had an extension to seven years with the primary endpoint of assessing the tolerance of denosumab.

3.1.1. Efficacy data concerning fracture prevention compared with placebo

The efficacy of denosumab in preventing fractures in postmenopausal osteoporosis was mainly evaluated in a pivotal phase III placebo-controlled study, the FREEDOM study described below.

FREEDOM[2] study (August 2004 to June 2008)

Primary outcome measure:
Demonstrate the superiority of denosumab compared with placebo in terms of reduction in the number of new vertebral fractures after three years of treatment.

Design:
Placebo-controlled, randomised, double-blind study.
This product should have been assessed against an active comparator such as a bisphosphonate rather than against placebo.

Inclusion criteria:
Postmenopausal women aged 60-90 years with osteoporosis defined by a lumbar spine or total hip T-score < -2.5.

Non-inclusion criteria included:
- Patients with a spine or hip T-score < -4,
- Any severe vertebral fracture[3] or more than two moderate vertebral fractures[3],
- Patients who had received an antiosteoporosis agent in the last three years.

Treatments:
The 7868 randomised patients were treated for three years with a subcutaneous injection every six months of either denosumab (n = 3933) or placebo (n = 3935). They all received calcium and vitamin D supplementation (≥ 1 g of calcium daily and ≥ 400 IU of vitamin D daily). The population was stratified in four groups according to patient age:

- 60-64 years
- 65-69 years
- 70-74 years
- ≥ 75 years

[1] Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months
[2] Cummings S R et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009; 361 (8): 756-765

[3] Prevalent vertebral fractures at inclusion and incident fractures throughout the trial were assessed by spine radiographs read centrally. They were classified using the Genant semi-quantitative scoring method:
- Grade 0 (normal vertebra)
- Grade 1 (minor fracture): 20-25% reduction in vertebral body height
- Grade 2 (moderate fracture): 25-40% reduction in vertebral body height
- Grade 3 (severe fracture): > 40% reduction in vertebral body height

Primary efficacy endpoint: Incidence of new vertebral fractures after three years of treatment.

Secondary endpoints included:

- time to onset of the first nonvertebral fracture,
- time to onset of the first hip fracture,

Results:
Of the 7868 patients included in the randomisation, 60 (29 in the placebo group and 31 in the denosumab group) were not included in the analysis; one investigation centre was closed following an inspection in view of the lack of reliability of data collected.
The principal demographic and clinical characteristics were similar in both treatment groups (see Table 1). Mean age was 72.3 years, mean lumbar spine T-score was -2.82 ± 0.70 and mean total hip T-score was -1.89 ± 0.81.
A clinical history of fracture (all types) was found in the medical record for 53.5% of patients in the FREEDOM study (including 38.8% nonvertebral fractures).[4]
The radiographs performed at inclusion showed that 23.6% of patients had a low prevalence of vertebral fractures. The proportion of patients with a history of femoral neck fracture was 2%, which indicates a low level of fracture risk in the population enrolled in this study.

Table 1. Patient characteristics at inclusion

	Placebo N =3906	Denosumab N=3902
Mean age (years)	72.3 ± 5.2	72.3 ± 5.2
Age group - n (%)		
60 - 64 years	208 (5.3)	206 (5.3)
65 - 69 years	820 (21.0)	824 (21.1)
70 - 74 years	1642 (42.0)	1637 (42.0)
≥ 75 years	1235 (31.7)	1236 (31.6)
Years since menopause (Mean)	24.2 ± 7.5	24.2 ± 7.4
Prevalent vertebral fractures n (%)		
Yes	915 (23.4)	929 (23.8)
No	2854 (73.1)	2864 (73.4)
Mean T-score at inclusion		
Lumbar spine	-2.84 ± 0.69	-2.82 ± 0.7
Hip	-1.91 ± 0.81	-1.89 ± 0.81
Femoral neck	-2.17 ± 0.71	-2.15 ± 0.72

About 83% of patients completed the three-year study period; the main reason for discontinuation of treatment was withdrawal of consent (10.3% in the placebo arm and 8.8% in the denosumab arm). The outcome of patients who discontinued treatment was not reported.

The analysis of the results included 94.7% of the randomised population, i.e. 7393 patients who had a radiograph at inclusion and at least one further visit after inclusion.

[4] Clinical study report, not given in the published study report

- Effect on vertebral fractures (primary efficacy endpoint)

Results are shown in Table 2. The superiority of denosumab over placebo was demonstrated: the absolute reduction in vertebral fracture incidence at three years compared with placebo was 4.8%, p<0.001.

Table 2. Incidence of vertebral fractures at three years

	Placebo N = 3691	Denosumab N = 3702	Absolute reduction in fracture incidence as % (CI)
patients with at least one new vertebral fracture after three years of treatment n (%)	264 (7.2%)	86 (2.3%)	4.8 (3.9; 5.8) p < 0.001

Source: Clinical study report

- Effect on nonvertebral and femoral neck fractures (secondary endpoints)

Median time to onset of the first nonvertebral or femoral neck fracture (time at the end of which 50% of patients had had a fracture) was not estimated as fewer than 10% of patients had a fracture during the three-year study follow-up period. Incidences of nonvertebral and femoral neck fractures at three years were estimated using the Kaplan-Meier method. Denosumab was superior to placebo in terms of reduction in incidence of nonvertebral fractures including femoral neck fractures, (see Table 3). The absolute reduction in risk of femoral neck fracture compared with placebo was 0.5% and the reduction in risk of nonvertebral fracture was 1.5%.

Table 3: Estimation of the incidence of nonvertebral and femoral neck fractures (Kaplan-Meier).

	Placebo N =3906	Denosumab N = 3902	Absolute reduction in fracture incidence as %
Number of patients with at least one new nonvertebral fracture after three years of treatment n (%)	293 (8)	238 (6.5)	1.5, 95% CI [0.3; 2.7] p = 0.01
Number of patients with at least one new femoral neck fracture after three years of treatment n (%)	43 (1.2)	26 (0.7)	0.5, 95% CI [0; 0.9] p = 0.04

- Sub-group analyses:

Two subgroup analyses, one scheduled and the other post-hoc, were included in the dossier.

The analysis scheduled in the FREEDOM study protocol was performed in the subgroup of patients with two of the following three criteria: age > 70 years, T-score ≤ -3, at least one vertebral fracture at inclusion.

In all, 45% of the population of the FREEDOM study, i.e. 3513 patients, were identified as satisfying these criteria. Characteristics of these patients were: mean age 74.8 ± 4.4 years (compared with 72.3 years in the global trial population), 45% had at least one vertebral fracture at inclusion (compared with 23.6% of the global population) and 36.2% had a nonvertebral fracture (compared with 38.8% of the global population). No patients had a history of femoral neck fracture. Lumbar spine T-score was -3.03 ± 0.71 (compared with -2.83 ± 0.69 in the global population) and femoral neck T-score was -2.43 ± 0.68 (compared with -2.16 ± 0.72 in the global population).

Denosumab was superior to placebo in terms of reduction in the risk of vertebral fracture (the incidence of vertebral fractures at three years was 10% with placebo compared with 3.5% with denosumab, i.e. an absolute reduction of 6.5% [4.8; 8.2]. p<0.0001) and of hip fracture (the incidence of hip fractures at three years was 2.1% with placebo compared with 1.1% with denosumab, i.e. an absolute reduction of 1% [0.2; 1.9], p = 0.02).

However, no difference was found between denosumab and placebo with regard to reduction in the risk of nonvertebral fracture (incidence of nonvertebral fractures at three years was 9.3% with placebo compared with 8.3% with denosumab, i.e. an absolute reduction of 1% [-1; 3.0], p = NS).

The scope of the results of this analysis in the "at very high risk of fracture" subgroup is limited in view of the non-inclusion in the FREEDOM study of severe forms of osteoporosis: T-score < -4, more than two moderate vertebral fractures or more than one severe vertebral fracture, and patients at risk of hip fracture (previous hip fracture found in only 2% of patients enrolled). In addition, the analysis was performed without the use of a statistical method to control alpha risk inflation.

Post-hoc analysis

A post-hoc analysis assessed reduction in the risk of femoral neck fracture in the subgroup of patients aged over 75 years who represented 31.6% of the global population. The mean age of these patients was 78.2 ± 3 years, and 27.6% had a history of vertebral fracture at inclusion. The incidence of femoral neck fractures at three years was 2.3% in the placebo group compared with 0.9% in the denosumab group i.e. an absolute reduction in risk of femoral neck fracture compared with placebo in these patients of 1.4%; 95% CI [0.4; 2.5], p<0.01. In all, this post-hoc subgroup analysis performed without adjustment of the alpha risk was an exploratory analysis.

Special population: patients with renal impairment

In a pharmacokinetic study (phase I) carried out in 55 patients with various degrees of renal impairment, including seven patients on dialysis and seven with creatinine clearance < 30 mL/min, the degree of renal impairment had no effect on the pharmacokinetics of denosumab. Therefore no dosage adjustment is needed in these patients. However, this trial did not show that the efficacy of denosumab in terms of fracture prevention was maintained in patients with renal impairment.

Data from the FREEDOM study extension: Study 20060289

An open extension of the FREEDOM study to seven years is currently in progress (i.e. up to ten years' follow-up of treatment with denosumab), with a primary endpoint of evaluating the tolerance of denosumab in patients with postmenopausal osteoporosis.

The results of a predefined intermediate analysis of this extension phase at two years are shown below. These results were not available when the Marketing Authorisation was approved and they have not yet been published (company's internal interim report).

Two cohorts were followed-up:

- patients previously randomised to the denosumab arm of the FREEDOM trial (n = 2343 i.e. 71.6% of the patients enrolled in the denosumab arm in the FREEDOM trial). This cohort had a maximum follow-up of five years of treatment at the time of the interim analysis at two years.
- patients previously randomised to the placebo arm of the FREEDOM trial (n = 2207 i.e. 68.8% of patients in the placebo arm of the FREEDOM trial) who had a maximum follow-up of two years of treatment.

All patients had one subcutaneous injection of denosumab 60 mg every six months and took daily vitamin and calcium supplements (≥ 1g of calcium and ≥ 400 IU of vitamin D).

After two years of follow-up, 1946 (83.1%) patients were continuing treatment and 397 (16.9%) patients had discontinued treatment. The most common reason for discontinuation was withdrawal of consent (5.7%). Adverse events were recorded for 2% of patients and death in 1.2%. As tolerance was the primary endpoint, it will be described in the relevant section 3.2.

After two years of treatment with denosumab, the incidence of new vertebral fractures was:

- 2.8% i.e. 59/2100 patients in the cohort of patients treated for a total of five years with denosumab.
- 1.7% i.e. 34/1978 patients in the cohort treated for two years with denosumab.

3.1.2. Efficacy data for BMD (intermediate criterion) compared with comparator

In two studies of similar design: DECIDE[5] (20050141 carried out between April 2006 and December 2007) and STAND[6] (20050234 carried out between October 2006 and March 2008), denosumab 60 mg was compared with alendronate 70 mg for the intermediate criterion total hip BMD. The primary efficacy endpoint of these studies was to demonstrate the noninferiority and if appropriate the superiority of denosumab over alendronate in terms of change in total hip BMD after one year of treatment in postmenopausal women with low BMD. Patients in the STAND study had to have previously been treated for at least six months with alendronate 70 mg.

The assumption was that denosumab would be found to be noninferior to alendronate if the lower limit of the 95% confidence interval of the difference in terms of percentage BMD at one year between the two groups was higher than a threshold set at -1.22% in the DECIDE study and -0.35% in the STAND study.

In the DECIDE study, the threshold of noninferiority corresponded to a permitted maximum loss of 50% of the efficacy of alendronate. In the STAND study, carried out in patients who had previously been treated with alendronate, the threshold calculation was based on a comparison of data from two studies which had evaluated changes in BMD at one year in patients who had continued or discontinued alendronate after having received it for at least six months. The threshold was set at 50% of the lower limit of the (95%) confidence interval of the differences in change in BMD between patients who had continued and those who had discontinued alendronate.

The primary efficacy endpoint was percentage change in total hip BMD after 12 months of treatment.
The analysis of results concerned randomised patients who had at least one BMD measurement at inclusion and at least one measurement during the follow-up phase.

Mean age of patients in the DECIDE study was 64.4 (8.5) years and mean time since menopause was 17.1 years (10.0). Mean T-score was -1.72 (0.80) for total hip score and -2.57 (0.75) for the lumbar spine. Half the patients (49% denosumab and 51% alendronate) had a history of at least one prevalent fracture at inclusion.
Mean age of patients in the STAND study was 67.6 (7.8) years, mean time since menopause was 19.3 years (9.6) and median previous treatment with alendronate was 36 months (6 - 192 months). Mean total hip T-score was -1.8 and mean lumbar spine T-score was -2.63. The proportion of patients who had a history of at least one prevalent fracture at inclusion was 53% in the denosumab group and 47% in the alendronate group.

[5] Brown J P et al. Comparison of the effect of denosumab et alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. J Bone Miner Res. 2009; (1): 153-161.

[6] Kendler DL et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. J Bone Miner Res. 2010; 25 (1): 72-81.

The noninferiority of denosumab was demonstrated for the primary endpoint in both studies:

- STAND study (n = 504): mean change in total hip BMD was 1.90% with denosumab and 1.05% with alendronate; difference = 0.85% [0.44; 1.25].
- DECIDE study (n = 1189): mean change in total hip BMD was 3.5% with denosumab and 2.6% with alendronate; difference = 1% [0.7; 1.2].

The secondary analysis specified in the protocol demonstrated the superiority of denosumab over alendronate in terms of increase in total hip BMD ($p<0.0001$).
However, it is to be regretted that the somewhat intermediate criterion with little relevance, gain in bone mass, was chosen as primary efficacy endpoint in these two studies comparing denosumab with an active therapy. The choice of an efficacy criterion demonstrating efficacy against fractures would have been more useful. Consequently, the results submitted do not make it possible to assess the clinical benefit of denosumab compared with alendronate in terms of efficacy in preventing osteoporotic fractures.

3.1.3. Noncomparative efficacy data on BMD (intermediate criterion) from the FREEDOM study extension phase at two years

After five years of treatment with denosumab (three years in the FREEDOM trial followed by two years in the extension phase), BMD increased by:

- 13.7% in the lumbar spine at five years compared with baseline in the FREEDOM trial (i.e. a 3.3% increase during the extension phase compared with the end of the FREEDOM study).
- 7% in the total hip at five years compared with baseline in the FREEDOM study (i.e. a 1.3% increase during the extension phase compared with the end of the FREEDOM study).

3.1.4. Preference and satisfaction study: DAPS[7]

This was an open-label crossover study lasting two years, with the aim of assessing patient compliance with denosumab given as a subcutaneous injection every six months compared with alendronate 70 mg given orally every week. Only one-year results have been published.[8] The study was carried out in Canada and the United States.

In this study, 250 postmenopausal patients aged 55 years or over, with a T-score between -4.0 and -2.0 for the lumbar spine, total hip or femoral neck were randomised to receive either denosumab 60 mg SC every six months or alendronate 70 mg orally every week for one year (Period 1), then the other treatment the next year (Period 2).

The alendronate bottle had a medication event monitoring system cap that recorded when the cap was opened and closed. Patients were instructed not to open the bottle except to take alendronate (one tablet each time).

[7] Denosumab Adherence Preference and Satisfaction

[8] Kendler DL, McClung MR, Freemantle N, et al. Adherence, preference, and satisfaction of postmenopausal women taking denosumab or alendronate. Osteoporos Int. 2010 [Epub ahead of print]. (DOI 10.1007/s00198-010-1378-z)

Patients all received daily vitamin and calcium supplements (≥ 1 g of calcium and ≥ 400 IU of vitamin D).
The following patients were not included:

- patients who had already received antiosteoporosis agents (bisphosphonates, denosumab, strontium ranelate, parathormone (PTH) or its derivatives;
- contraindications to the use of alendronate;
- a symptomatic vertebral fracture in the three months before inclusion.

The primary endpoint was the proportion of patients adhering to treatment at the end of period 1 (one year). A patient was classed as adherent to denosumab therapy on three conditions:

- she had to have received two injections of denosumab;
- these two injections had to have been administered at six months (± four weeks) apart and;
- she had to have completed the first twelve months of the study.

For alendronate, a patient was classed as adherent to therapy if she had:

- taken ≥ 80% of the tablets prescribed and;
- taken at least two tablets during the last month and;
- completed the first twelve months of the study.

Results:
Mean T-scores for the population enrolled reflect clinical practice in the United States and Canada where the study was carried out. The population enrolled does not appear to be representative of the population treated in France. Details were not given of previous fractures at inclusion.
The open-label nature of the study is a limitation.

Table 4. Demographic and clinical characteristics of patients at inclusion - DAPS study.

	Alendronate 70 mg 1 tablet/week N = 124	Denosumab 60 mg 1 subcutaneous/6 months N = 126
Mean age (SD)	65.3 (7.7)	65.1 (7.6)
Years since menopause (SE)	17.2 (10.0)	18.2 (11.4)
T-score lumbar spine, mean (SD)	-1.89 (1.13)	-2.04 (1.16)
T-score total hip, mean (SD)	-1.60 (0.76)	-1.60 (0.74)
T-score femoral neck, mean (SD)	-2.03 (0.62)	-2.01 (0.55)

Of the 124 patients randomised to receive alendronate in period 1, 106 (85.5%) patients completed period 1 (one year of treatment). The reasons for early treatment discontinuation were mainly adverse effects (4%), loss to follow-up (4%) and withdrawal of consent (3.2%). Of the 126 patients randomised to receive denosumab, 114 (90.5%) completed period 1. The reasons for early treatment discontinuation were mainly withdrawal of consent (4.8%) and loss to follow-up (2.4%).

After one year of treatment, based on MEMS data, 76.6% (95/124) of patients had adhered to oral alendronate once weekly and 88.1% (111/126) of patients to denosumab SC every six months, i.e. a difference in compliance of 9.7%, 95% CI = [0.3; 19] between these two therapies.

The MEMS results were compared with the tablet count for alendronate: 76.6% (95/124) compliance from MEMS compared with 78.2% (97/124 patients) based on the tablet count ($r = 0.71$; $p<0.001$). No information was given on the use of an equivalent test for denosumab.

3.1.5. Elements from the indirect comparison of efficacy against fractures

In the absence of any studies comparing the efficacy of denosumab against fractures with that of other antiosteoporosis agents, the company proposed a meta-analysis of adjusted indirect comparisons[9] of the different therapies. Different types of inconsistencies of effects related to the statistical analysis were identified:

- inconsistency in the effect of strontium on vertebral fractures (radiological fractures included)
- inconsistencies in the effect of alendronate on wrist fractures
- inconsistencies in the effect of the oral bisphosphonates category
- inconsistencies in the effect of the IV bisphosphonates category

In view of these inconsistencies in effects, the comparison of denosumab with these drugs or categories would appear to be unreliable. In addition, the consistency of the network of comparisons was not formally tested. The results were not put into perspective, particularly in relation to the adverse events observed (a specific meta-analysis would have been needed).

In all, this meta-analysis only makes it possible to suggest by indirect comparison (and therefore with a lower level of evidence than that of a direct comparison) that there is no significant difference between denosumab and the other drugs with regard to preventing the most important fractures from a public health point of view (fractures of the upper end of the femur).

Table 5. Results of adjusted indirect comparisons (Source: internal company report)

	New vertebral (i.e. morpohometric) RR (95% CI)	Clinical vertebral RR (95% CI)	Nonvertebral RR (95% CI)	Hip RR (95% CI)	Wrist RR (95% CI)
Denosumab *versus* strontium	0.451 (0.324 - 0.627)	0.488 (0.299 - 0.796)	0.927 (0.755 - 1.138)	0.680 (0.388 - 1.192)	0.860 (0.575 - 1.286)
Denosumab *versus* raloxifene	0.501 (0.370 - 0.678)	0.700 (0.079 - 6.165)	1.235 (0.304 - 5.029)		
Denosumab *versus* teriparatide	0.936 (0.554 - 1.581)		1.733 (0.909 - 3.302)	2.408 (0.256 - 22.644)	2.931 (0.597 - 14.389)
Denosumab *versus* zoledronate	1.083 (0.779 - 1.505)	1.400 (0.733 - 2.673)	1.084 (0.870 - 1.351)	1.028 (0.569 - 1.859)	
Denosumab *versus* alendronate	0.576 (0.422 - 0.786)	0.698 (0.368 - 1.322)	0.954 (0.775 - 1.174)	0.929 (0.476 - 1.813)	1.036 (0.447 - 2.401)
Denosumab *versus* risedronate	0.525 (0.380 - 0.725)		1.008 (0.818 - 1.242)	0.815 (0.475 - 1.397)	1.248 (0.727 - 2.141)
Denosumab *versus* etidronate	0.700 (0.242 - 2.024)		0.205 (0.023 - 1.817)	0.204 (0.008 - 5.128)	0.170 (0.008 - 3.543)
Denosumab *versus* oral ibandronate (2.5 mg)	0.642 (0.408 - 1.011)	0.589 (0.305 - 1.138)	0.732 (0.525 - 1.021)		

[9] Unpublished. Internal report.

Analysis of the additional indirect comparison:

In the population concerned by this request for listing, i.e. :

- patients considered to have a very high risk of fracture, defined as patients satisfying at least two of the following three criteria: age ≥ 70 years, T-score ≤ -3 or at least one vertebral fracture
- patients with a contraindication, intolerance or failure of a treatment for postmenopausal osteoporosis,

no indirect comparison was performed with other treatments for osteoporosis. It is therefore difficult to assess the therapeutic contribution of denosumab in the population of interest claimed compared with the other available alternatives.

3.1.6. Efficacy data for BMD (intermediate endpoint) in the sub-populations of postmenopausal osteoporosis

HALT-BC[10] study (20040135); October 2004 and May 2007

Aim: to compare the efficacy of denosumab and placebo in terms of preservation of BMD in the lumbar spine in women with nonmetastatic breast cancer treated with an aromatase inhibitor.

Design:
Controlled, randomised, double-blind trial.

Inclusion criteria:
Women aged at least 18 years with adenocarcinoma of the breast confirmed cytologically or histologically, treated (or about to be treated) with an aromatase inhibitor, in good general health and with a lumbar spine, total hip and femoral neck BMD corresponding to a T-score between -1.0 and -2.5.

Non-inclusion criteria:
- Patients receiving concomitant systemic cancer therapy other than aromatase inhibitors,
- Patients with distant metastases, other malignant tumours or recurrence of the primary cancer,
- Patients receiving or having received other antiosteoporosis agents.

The EMA considered[11] that this population was included in the population of women with postmenopausal osteoporosis who were at increased risk of fractures.

Treatments:
Patients were stratified according to how long they had been using an aromatase inhibitor (less than six months or more than six months) and they were randomised to receive one subcutaneous injection of either denosumab or placebo every six months for two years. They all received calcium and vitamin D supplementation daily (≥ 1 g of calcium and ≥ 400 IU of vitamin D).

Primary efficacy endpoint:
Percentage change at one year in BMD in the lumbar spine compared with baseline value.

Results:

Baseline patient characteristics (see Table 4)

[10] Ellis GK, Bone HG, Chlebowski R et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. J Clin Oncol 2008; 26 (30): 4875-4882.
[11] EPAR

The principal demographic and clinical characteristics were similar in both treatment groups. Mean age of the 252 patients enrolled was 59.5 years, 63% of them had been treated with aromatase inhibitor for more than six months, they had gone through the menopause a mean of 12.8 years previously in the denosumab group and 13.1 years previously in the placebo group. Their mean lumbar spine T-score was -1.1 at inclusion. However, they did not all have osteoporosis in the sense of the WHO definition of osteoporosis (T-score less than or equal to -2.5) as the maximum T-score values reported for certain patients were +2.6 at lumbar spine, +0.9 at the total hip and +1.2 at the femoral neck. A very small proportion of patients had a history of vertebral fracture at inclusion: 8% in the denosumab group and 4% in the placebo group. From the characteristics of the patients included in the study, it was not clearly established that they were at increased risk of fracture.

Table 4. Patient characteristics at inclusion

	Placebo N=125	Denosumab N=127
Mean age (years)	59.7 ± 9.7	59.2 ± 8.9
Age group - n (%)		
35 - < 45 years	4 (3)	1 (1)
45 - < 55 years	37 (30)	40 (31)
55 - < 65 years	43 (34)	51 (40)
65 - < 75 years	32 (26)	29 (23)
> 75 years	9 (7)	6 (5)
Mean T-score at inclusion		
Lumbar spine	-0.98 ± 0.93	-1.13 ± 0.87
Hip	-0.88 ± 0.68	-1.02 ± 0.63
Femoral neck	-1.20 ± 0.66	-1.33 ± 0.66

Two hundred and forty-nine of the two hundred and fifty-two patients randomised took at least one dose of treatment. Approximately 83% of the patients treated with denosumab and 79% of those treated with placebo completed the two-year study period. Withdrawal of consent was the main reason for treatment discontinuation (20%).

The analysis included 97% (n = 245) of the randomised population, corresponding to patients for whom a baseline and final assessment of the endpoint were available.
Denosumab was superior to placebo in terms of increase in BMD at the lumbar spine after one year of treatment in women with nonmetastatic breast cancer who were treated with an aromatase inhibitor.

Table 5. Mean percentage change in T-score at the lumbar spine after one year compared with baseline value.

	Placebo N= 122	Denosumab N = 123
Mean T-score at inclusion	-0.98 ± 0.93	-1.13 ± 0.87
Change in T-score at the lumbar spine after one year (%, 95% CI)	-0.7 (-1.3; -0.1)	4.8 (4.3; 5.4)
Difference compared with placebo	5.5 (4.8; 6.3) p< 0.0001	

Source: Clinical trial report

In all, in view of the intermediate nature of the primary efficacy endpoint used (BMD) and the absence of demonstration of an effect in preventing fractures in this population, the results of this study alone do not make it possible to determine the actual benefit of denosumab in patients with nonmetastatic breast cancer who were treated with an aromatase inhibitor.

With regard to the comparison with placebo, a comparison with another antiosteoporosis agent in terms of efficacy against fractures would have been more useful, making it possible to establish the place of denosumab in relation to the available alternatives.

3.2. Efficacy in the treatment of bone loss associated with hormone ablation in men with prostate cancer.

The clinical dossier is based on one study:

HALT PC study[12] (20040138), carried out between August 2004 and May 2008

The efficacy of denosumab administered by a single subcutaneous injection every six months was assessed in comparison with placebo in 1468 men aged 48-97 years with nonmetastatic prostate cancer treated with androgen deprivation therapy. In addition, these patients were at increased risk of fractures, defined in the study as:

- age over 70 years or,
- age under 70 years with a T-score < -1 at the lumbar spine, the total hip or femoral neck, or previous osteoporotic fracture.

The following patients were not included:

- patients with prostate cancer metastases,
- patients who had had either radiotherapy, or chemotherapy other than hormone therapy, and those whose PSA concentration was still higher than 5 ng/mL after one month of hormone ablation therapy;
- patients with a T-score under -4;
- patients who had been treated with IV bisphosphonates during the previous five years;
- patients who were unable to walk (ECOG performance status higher than 2).

These noninclusion criteria mean that the population is unlikely to be representative of the population treated in real life.

Design:
Placebo-controlled, randomised, double-blind study.

Patients were randomised to receive either denosumab or placebo for three years. The randomisation was stratified by age group (under or over 70 years) and by duration of hormone deprivation therapy at inclusion (under or over six months). All patients received calcium (at least 1000 mg) and vitamin D (at least 400 IU) supplementation.
The number of subjects needed was calculated to assess the effect of denosumab of BMD and on fracture incidence

Primary efficacy endpoint:
Percentage change from baseline BMD value at the lumbar spine after two years of treatment.

Secondary endpoints were:

- incidence of fractures irrespective of site, including vertebrae, excluding the skull, face, mandible, fingers and toes
- incidence of new vertebral fractures at three years

[12] Smith MR et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl J Med 2009; 361 (8): 745-755.

[12] Smith MR et al. Effects of Denosumab on Bone Mineral Density in Men Receiving Androgen Deprivation Therapy for Prostate Cancer. J Urol 2009; 182: 2670-2676.

The most useful endpoint, i.e. reduction in fracture incidence, was only evaluated as a secondary endpoint.

Results:

Characteristics of the patients included:

The principal demographic and clinical characteristics were similar in both treatment groups (see Table 7). Mean patient age was 75.4 years. Approximately 78% of patients had a T-score < -1 at the lumbar spine or femoral neck. However, some patients had higher T-score values at inclusion, i.e. maximum values of +7.6 at the lumbar spine, +3.3 at the total hip and +3 at the femoral neck. Only 14.3% of patients in the denosumab group and 15.1% of patients in the placebo group had osteoporosis according to the WHO definition (T-score less than or equal to -2.5) and only 21% of patients in the denosumab group had a history of vertebral fracture at inclusion.

Table 7. Characteristics of the population included

	Placebo (N = 734)	Denosumab (N = 734)
Mean age (years)	75.5 ± 7.1	75.3 ± 7.0
Age group - n (%)		
< 50 years	0 (0.0)	1 (0.1)
50 - 59 years	20 (2.7)	23 (3.1)
60 - 69 years	103 (14.0)	100 (13.6)
70 - 79 years	396 (54.0)	405 (55.2)
80 - 89 years	205 (27.9)	197 (26.8)
> 90 years	10 (1.4)	8 (1.1)
Previous fracture		
Yes	174 (23.7)	155 (21.1)
No	504 (68.7)	531 (72.3)

One of the limitations of this study was the large number of treatment discontinuations: approximately 64% of patients in the denosumab group and 61% of patients in the placebo group completed the three years of the study; withdrawal of consent was the main reason for treatment discontinuation (18.4%). In addition, results were not analysed by ITT but only in patients who had one or more radiographic assessments (i.e. 92.5% of patients in the denosumab group and 91.7% of those in the placebo group).

Effect on BMD (primary efficacy endpoint)

After two years of treatment, a significant increase was observed in BMD at the lumbar spine with denosumab (+5.6%) compared with placebo (-1.0%) i.e. a difference of 6.7 (6.2; 7.1). $p<0.0001$ (see Table 8). A significant increase in BMD after two years of treatment was demonstrated for denosumab compared with placebo at the total hip (4.8%) and at the femoral neck (3.9%), $p<0.001$.

Table 8. Change in BMD at the lumbar spine at two years (primary efficacy endpoint)

	Placebo	Denosumab
Mean T-score at inclusion	N = 729 -0.4 ± 1.8	N = 727 -0.3 ± 1.8
Change in lumbar spine T-score at two years (%, 95% CI)	N = 716 -1 (-1.4; -0.7)	N = 714 5.6 (5.3; 5.9)
Difference compared with placebo	6.7 (6.2; 7.1); p< 0.0001	

Effect on fractures (secondary endpoints)

No difference was demonstrated between denosumab and placebo on incidence of fractures taking all sites together at three years: 7.2% in the denosumab group compared with 5.2% in the placebo group, p=NS. Denosumab was superior to placebo for reduction in the incidence of vertebral fractures at three years. The incidence of vertebral fractures at three years was 1.5% in the denosumab group compared with 3.9% in the placebo group. i.e. a difference of 2.4%, p<0.006. However, the difference observed was minimal and its clinical importance was debatable. In addition, no difference between denosumab and placebo was observed for prevention of fractures at sites other than the spine.

Discussion of results of the HALT PC study

Interpretation of the results of this study is difficult for the following reasons:

- the high proportion of treatment withdrawals (approximately 38%);
- the absence of demonstration of superiority of denosumab compared with placebo for reduction of femoral neck fractures;
- the debatable clinical importance of the very small difference observed in reduction in incidence of vertebral fractures compared with placebo (2.4%),
- the inclusion and noninclusion criteria for the study and the characteristics of patients enrolled, which do not allow the results to be translated into real-life practice.

In view of these factors, the actual benefit of denosumab compared with bisphosphonates cannot be assessed from the dossier as it currently stands.

3.3. Adverse effects

3.4.1. Data from clinical studies

The tolerance of PROLIA (denosumab) in clinical studies has been evaluated in more than 10 000 patients who received at least one dose of treatment. In the treatment of postmenopausal osteoporosis, the maximum period of treatment is five years (FREEDOM study extension). In view of its mechanism of action, special attention has been paid to the incidence of complications in the form of infection and cancer.

Infection:

In two clinical studies with small populations (314 patients treated with denosumab compared with 46 treated with placebo in one study and 164 patients treated with denosumab compared with 165 treated with placebo in another) carried out in postmenopausal osteoporosis, the incidence of adverse events in the form of infection leading to hospitalisation was higher in the denosumab group than in the placebo group (4.9% compared with 0.6% in one study and 3.2% compared with 0% in another). Infection was generally in the form of pneumonia, urinary infection, cellulitis or diverticulitis.

In the large scale FREEDOM study (approximately 7900 patients) carried out in osteoporosis, there were 4.1% serious adverse events in the form of infection in the PROLIA group compared with 3.4% in the placebo group. The annual incidence of serious adverse events in the form of infection expressed per 100 patient-years during follow-up was:

- 1.7 for denosumab and 1.2 for placebo in the first year
- 1.9 for denosumab and 1.6 for placebo in the second year
- 1.8 for denosumab and 1.5 for placebo in the third year
- 1.5 for denosumab in the fourth year
- 1.4 for denosumab in the fifth year

Specifically concerning serious skin infections that led to hospitalisation, such as cellulitis caused by infection or erysipelas, during the three years of the FREEDOM study, twelve cases were reported in the denosumab group compared with a single case in the placebo group. There was no increase in the incidence of cellulitis and erysipelas with hospitalisation during the extension phase of the FREEDOM study (less than 0.1 event per 100 patient-years at four and five years). Furthermore, the incidence of serious skin infections (requiring hospitalisation) was similar in both placebo and denosumab groups (0.6% in each group) during trials carried out in breast and prostate cancer.

For diverticulitis, in a study carried out in men receiving hormone ablation therapy for prostate cancer, an increased incidence of diverticulitis was reported, i.e. 1.2% for denosumab compared with 0% for placebo. This difference was not found in phase III studies carried out in postmenopausal osteoporosis, when the incidence of diverticulitis was 0.8% for denosumab and 0.6% for placebo.

No increase in opportunist infection was observed during the studies.

Cataract:
An increased incidence of cataract was reported in a study carried out in men receiving hormone ablation therapy for prostate cancer, i.e. 4.7% for denosumab compared with 1.2% for placebo. The majority of these events occurred during the first year of treatment and the proportion of patients with previous cataract at inclusion was high, i.e. 38.2% in the denosumab group compared with 22.2% in the placebo group. The differences were not observed in other studies carried out in postmenopausal osteoporosis; in these studies the incidence of cataract was 5.8% for denosumab compared with 6.3% for placebo..

<u>Cancer</u>
In the study carried out in men with prostate cancer, the incidence of neoplasm was higher for denosumab (16.3%) than for placebo (11.9%). No difference in global incidence of cancer was reported in the other studies. In two studies carried out in postmenopausal osteoporosis, cancer was reported as a serious adverse event in 4% of patients treated with denosumab compared with 3.5% of patients treated with placebo.

In the FREEDOM study, the incidence of cancer events at three years was 4.8% for denosumab and 4.3% for placebo.

The annual incidence of cancer events expressed per 100 patient-years during follow-up was:

- 1.8 for denosumab and 1.8 for placebo in the first year
- 1.4 for denosumab and 1.5 for placebo in the second year
- 2.1 for denosumab and 1.4 for placebo in the third year
- 1.8 for denosumab in the fourth year
- 2.1 for denosumab in the fifth year

<u>Other adverse events:</u> osteonecrosis of the jaw

Two cases[13] of osteonecrosis of the jaw (ONJ) were reported in patients treated with denosumab for postmenopausal osteoporosis. Warnings about this are given in the SPC.

Monitoring of the risk of infection requiring hospitalisation (particularly skin infection), osteonecrosis of the jaw, hypocalcaemia, and cancer is included in the risk management plan.

3.4.2. Data from clinical experience (PSUR 1 at six months)

Between 26 May 2010 and 26 November 2010, i.e. six months after denosumab was placed on the market, there was a total of 7826 patient-years of exposure to denosumab worldwide (with 3633 in Europe).
In patients treated with denosumab 60 mg (PROLIA) every six months for postmenopausal osteoporosis (PMO), there were three confirmed cases of ONJ in clinical trials. There have been no confirmed cases of ONJ post-marketing.

In patients treated with a higher dose of denosumab (120 mg every four weeks for various forms of cancer), there were 111 confirmed cases of ONJ in the clinical trials. There have been no reported cases of ONJ post-marketing to date during use of the higher dosage of denosumab in oncology.
During this period, four cases of cellulitis leading to hospitalisation (one in the indication of PMO, and three with an unknown indication) have been reported.

This first PSUR was analysed by the EMA in April 2011 and has not led to any change being made to the SPC for PROLIA.

3.4.3. Monitoring of potential and identified risks

The European risk management plan (RMP) includes monitoring of the following potential adverse events: hypocalcaemia, osteonecrosis of the jaw (ONJ), skin infection causing hospitalisation, complications of fractures, infection, hypersensitivity reactions, cataracts in men with prostate cancer who are receiving hormone ablation therapy, cardiovascular events, cancer, immunogenicity, atypical fractures, osteonecrosis at a site other than the jaw (avascular necrosis), and pancreatitis. Of these events, hypocalcaemia, skin infection causing hospitalisation and osteonecrosis of the jaw have been defined as identified risks for which special monitoring by specific questionnaires has been set up.

The PROLIA RMP also includes the setting up of an observational study in patients with prostate cancer to evaluate the incidence of cataract.

As part of the post-Marketing Authorisation monitoring of PROLIA in France, the company plans to carry out a two-year observational study whose primary endpoints will be to describe the characteristics of patients treated (age, severity of osteoporosis, etc.), their management (diagnosis, treatment, new fractures, reasons for treatment withdrawals, etc.), and the incidence of adverse events (prospective recording of certain adverse effects of particular interest such as infection).

[13] Judged to be positive by an independent committee established by the company

3.4. Conclusion

Postmenopausal osteoporosis

Efficacy:
Denosumab 60 mg (PROLIA) administered as a subcutaneous injection every six months was compared with placebo in the FREEDOM study in 7868 women with postmenopausal osteoporosis, mean age 72.3 years and with a mean T-score at the lumbar spine of -2.83 ± 0.69 and at the total hip of -1.90 ± 0.81. Only 23.6% of the patients had a previous vertebral fracture at inclusion. The primary efficacy endpoint was incidence of new vertebral fractures while the incidence of nonvertebral fractures, including femoral neck fractures, was only evaluated as a secondary endpoint. After three years of treatment, the incidence of vertebral fractures was lower with denosumab 60 mg (2.3%) than with placebo (7.2%); this reduction was modest (4.8% 95% CI [3.9 ; 5.8]. $p<0.001$). Denosumab was also superior to placebo for reduction in risk of nonvertebral fractures (absolute reduction of 1.5% [0.3 ; 2.7], $p=0.01$) and fractures of the femoral neck (absolute reduction of 0.5% 95% CI [0 ; 0.9], $p=0.04$).

The choice of certain noninclusion criteria (previous severe vertebral fracture, history of more than two moderate vertebral fractures or T-score < -4) which limited the transferability of results to the most at-risk patients is regrettable. The choice of placebo as comparator is not useful as there are other medicines which have been shown to be effective in preventing both vertebral and peripheral fractures, including femoral neck fractures.
In the absence of a direct comparison, the company offered adjusted indirect comparisons of the efficacy against fractures of denosumab compared with that of different antiosteoporosis agents. Taking account of the demonstration of inconsistencies in certain comparisons, the results of this meta-analysis suggest there is no difference in efficacy between denosumab and the other drugs available, particularly for the prevention of femoral neck fractures. Tolerance was not compared in this meta-analysis.

Two studies compared denosumab and alendronate, with BMD as the primary endpoint, including one study carried out in patients previously treated for at least six months with alendronate (STAND study). Another study compared denosumab with placebo in terms of change in BMD in patients with nonmetastatic breast cancer treated with an aromatase inhibitor. It should be remembered that BMD is only an intermediate endpoint.

A study carried out in 55 patients with renal impairment (seven on dialysis and seven with creatinine clearance < 30 mL/min), which is a contraindication to the other antiosteoporosis agents, notably bisphosphonates, strontium ranelate and teriparatide, showed that no adjustment of the dosage of denosumab was required. However, it was not shown that the effect of denosumab on gain in bone mass and prevention of fractures was maintained in this situation.

It was not shown that the level of compliance was better with denosumab than with the available alternatives.

So finally, in view of:

- the demonstration of efficacy compared with placebo in preventing both vertebral fractures and femoral neck fractures,
- items in the indirect comparison suggesting that the efficacy of denosumab is similar to that of the other available drugs, particularly in preventing femoral neck fractures,
- the demonstration of its efficacy compared with a bisphosphonate (alendronate) after bisphosphonate therapy in terms of increasing bone mineral density,

and on the other hand, the uncertainties about its long term tolerance,

the Transparency Committee considers that the actual benefit of denosumab, with the dossier as it currently stands, is as second-line therapy after bisphosphonates.

Adverse effects:
In two studies with small populations, the incidence of adverse events in the form of infection leading to hospitalisation (pneumonia, urinary infection, cellulitis and diverticulitis) was higher in the denosumab group than in the placebo group (4.9% with denosumab compared with 0.6% with placebo in a study in 329 patients and 3.2% with denosumab compared with 0% with placebo in another study in 314 patients treated with denosumab and 46 receiving placebo).

In the large scale FREEDOM study (approximately 7900 patients), the percentage of serious adverse events in the form of infection was 4.1% in the PROLIA group compared with 3.4% in the placebo group. The annual incidence of serious adverse effects in the form of infection expressed per 100 patient-years during follow-up was:

- 1.5 for denosumab and 1.1 for placebo in the first year
- 1.6 for denosumab and 1.4 for placebo in the second year
- 1.6 for denosumab and 1.4 for placebo in the third year
- 1.3 for denosumab in the fourth year
- 1.2 for denosumab in the fifth year

There was no increase in cases of opportunist infection.

In the FREEDOM study, the incidence of cancer events at three years was 4.8% with denosumab and 4.3% with placebo. The annual incidence of cancer events expressed per 100 patient-years was relatively constant:

- 1.8 for denosumab and 1.8 for placebo in the first year;
- 1.4 for denosumab and 1.5 for placebo in the second year
- 2.1 for denosumab and 1.4 for placebo in the third year
- 1.8 for denosumab in the fourth year
- 2.1 for denosumab in the fifth year

Three cases of osteonecrosis of the jaw (two of which were confirmed by the independent committee) were reported during clinical trials in patients treated for postmenopausal osteoporosis with denosumab 60 mg (PROLIA).

No new notifications occurred during pharmacovigilance monitoring covering six months of denosumab being marketed worldwide.

The risk management plan for denosumab includes monitoring these identified and potential risks (in particular, skin infection, hypocalcaemia, cancer and osteonecrosis of the jaw).

There are limited long term tolerance data.

Bone loss associated with hormone ablation therapy in men with prostate cancer

Efficacy:
The efficacy of denosumab administered as a subcutaneous injection every six months was evaluated in men with nonmetastatic prostate cancer treated with androgen deprivation therapy and at increased risk of fracture defined in the study as age > 70 years or, < 70 years and T-score < -1 at the lumbar spine, at the total hip or at the femoral neck, or previous osteoporotic fracture.
Mean age of patients included was 75.4 years. Approximately 78% of patients had a T-score < -1 at the lumbar spine or femoral neck. However, some patients had higher T-score values at inclusion, i.e. maximum values of +7.6 at the lumbar spine, +3.3 at the total hip and +3 at the femoral neck. Only 14.3% of patients in the denosumab group and 15.1% of patients in the placebo group had osteoporosis according to the WHO definition (T-score less than -2.5) and only 21% of patients in the denosumab group had a history of vertebral fracture at inclusion.
Approximately 36% of patients in the denosumab group and 39% of patients in the placebo group discontinued the study prematurely.
After two years of treatment, BMD at the lumbar spine (primary efficacy endpoint) had increased more under denosumab (5.6 95% CI [5.3; 5.9]) than under placebo (-1 95% CI [-1.4; -0.7]) i.e. an absolute gain of 6.7% 95% CI [6.2; 7.1], p<0.0001. There was no difference in incidence of fractures taking all sites together at three years (secondary endpoint) between denosumab (7.2%) and placebo (5.2%) p=NS. Denosumab was superior to placebo in reducing the incidence of vertebral fractures at three years (1.5% compared with 3.9%, p<0.006), but this difference was minimal (2.4%) and its clinical relevance debatable. In addition, no difference between denosumab and placebo was observed for prevention of fractures at sites other than the spine.
However, the severity of osteoporosis is related most of all to fractures of the upper end of the femur.
Overall, in view of:

- the inclusion and noninclusion criteria for the study and the characteristics of patients enrolled which do not allow the results to be translated into real-life practice.
- the high proportion of treatment withdrawals (approximately 38%);
- the absence of demonstration of superiority of denosumab compared with placebo for reduction of femoral neck fractures;
- the dubious clinical relevance of the minimal difference (2.4%) in reduction of incidence of vertebral fractures with denosumab compared with placebo,

it is difficult to assess the actual benefit of denosumab compared with the bisphosphonates used in everyday practice with the dossier as it currently stands.
It should be noted that the company has developed another proprietary medicinal product containing denosumab called Xgeva 120 mg solution for injection which on 19 May 2011 obtained a centralised Marketing Authorisation for the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours.

Adverse effects:
There are limited long term tolerance data.

In a study carried out in men treated with hormone ablation therapy for prostate cancer, the incidence of diverticulitis (1.2% compared with 0%) and of cataract was higher for denosumab than for placebo (4.7% compared with 1.2%). In the study carried out in men with prostate cancer, the incidence of neoplasm was higher with denosumab (16.3%) than with placebo (11.9%). In patients treated with a higher dose of denosumab (120 mg every four weeks) for various forms of cancer, there were 111 confirmed cases of ONJ in the clinical trials. No cases were reported during post-marketing monitoring.

The risk management plan for denosumab includes monitoring of these identified and potential risks (in particular, skin infection, cancer and osteonecrosis of the jaw).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Postmenopausal osteoporosis in women with an increased fracture risk

Osteoporosis is a serious disorder because of the risk of fractures. In particular, fractures of the femoral neck can be life-threatening.

PROLIA is a drug to prevent osteoporotic fractures in patients with increased fracture risk. It has been shown to be effective in reducing the risk of vertebral and peripheral fractures including femoral neck fractures.

The efficacy/adverse effects ratio is high. However, there are uncertainties about its long term tolerance. The identified and potential risks that are the subject of special monitoring are specifically infection, cancer and osteonecrosis of the jaw.

In the absence of any demonstration of its superiority over bisphosphonates whose role is well established in the treatment of postmenopausal osteoporosis and uncertainties about its long term tolerance, but in view of the demonstration of efficacy after bisphosphonate therapy, the Transparency Committee considers that the role of PROLIA is as second-line therapy after bisphosphonates in this indication.

Public health benefit
In view of the high prevalence of postmenopausal osteoporosis (25% of women aged +65 years and 50% of women aged +80 years) and the severity of its consequences (related to fractures, their complications and the associated disability and/or incapacity), the public health burden of osteoporosis is substantial.
Improvement in the management of postmenopausal osteoporosis is a public health need which is an established priority (French law of 9 August 2004 on public health policy, Objective 82: reducing fractures of the upper end of the femoral neck).

In view of the clinical data available on the incidence of fractures obtained from placebo-controlled studies and indirect comparisons and from studies using an intermediate endpoint (change in BMD) against an active comparator, PROLIA can be expected to have only a small additional impact on morbidity in treated patients compared with existing alternative therapies. Nevertheless, PROLIA could contribute an additional response to the need for management of patients after bisphosphonates.
However, as it is not certain that the results of studies can be translated into practice in view of the populations studied (few patients with a history of fracture, exclusion of patients at very increased risk of fractures, severe fractures) which are different from the populations for whom bisphosphonates are currently recommended for reimbursement.

The presumed impact of the proprietary medicinal product on the health system in terms of reduction of admissions to hospital and to an institution of elderly subjects has not been established.

Consequently, in the current state of knowledge and in view of the fact that other therapies are already available, it is not expected that PROLIA will benefit public health in this indication.

There are treatment alternatives.

The actual benefit of PROLIA is substantial in the second-line treatment of postmenopausal osteoporosis after bisphosphonates.

Bone loss associated with hormone ablation therapy in men with prostate cancer

In men with prostate cancer, hormone ablation therapy can cause bone loss, which is serious in view of the fracture risk. In particular, fractures of the femoral neck can be life-threatening.

This proprietary medicinal product is a preventive therapy against osteoporotic vertebral fractures in patients with prostate cancer who are treated with hormone ablation therapy.

In a clinical study, denosumab was shown to be superior to placebo in terms of increasing bone mass and preventing vertebral fractures. However, the clinical importance of the difference observed in comparison with placebo (for vertebral fractures) is debatable. Its efficacy has not been demonstrated in preventing femoral neck fractures, the most important objective. In addition, the inclusion and noninclusion criteria for the study and the characteristics of patients included do not make it possible to translate the results into real life practice.
In view of all these factors, the clinical contribution of denosumab has not been demonstrated in the current state of the dossier.
In addition, in terms of tolerance, notifications were found in the study provided in this indication (high incidence of neoplasms, onset of diverticulitis and cataract). Consequently, uncertainties remain about the long term tolerance of this medicinal product. In the current state of the dossier, no efficacy/adverse events ratio can be established.

Public health benefit:

The public health burden related to bone loss associated with hormone ablation therapy when prescribed to men with prostate cancer can only be low.

Improvement in the management of bone loss in this situation is a public health need which is an established priority (French law of 9 August 2004 on public health policy, Objective 82: reducing fractures of the upper end of the femoral neck, Cancer Plan).

There are few available data that could be used to judge in advance the potential impact of PROLIA, i.e. a single clinical trial with an intermediate endpoint (change in BMD). The expected impact of PROLIA can only be small and, in particular, no impact can be expected on morbidity in treated patients in terms of reduction of femoral neck fractures. In addition, it is not certain that the results of this study can be translated into clinical practice (particularly in view of the restriction of the study population to nonmetastatic patients on androgen deprivation therapy). The profile of patients treated in everyday practice is likely to be different from that of patients in the study. There are no data that would make it possible to anticipate any impact from PROLIA on the health system.

So there is nothing that would allow us to assume that PROLIA would contribute any additional response to an identified need.

Therefore, in the current state of knowledge, no public health benefit is expected for PROLIA in this indication.

There are treatment alternatives, particularly bisphosphonates which are used in current practice and which have demonstrated their effect on bone mass, but which have not formally proved their efficacy in preventing fractures. Nevertheless, the IV forms are indicated for the prevention of skeletal complications in patients with bone metastases (patients who were not included in the study that evaluated denosumab).

In view of the weekly administration regimen of PROLIA, when androgen deprivation therapy is stopped, there are concerns that the duration of exposure of patients to PROLIA would be

higher than that of the hormone deprivation therapy, and therefore unjustified in view of the uncertainties about its tolerance.

In view of all these factors, the actual benefit of PROLIA is insufficient in relation to existing therapies to justify reimbursement by National Health Insurance.

4.2. Improvement in actual benefit (IAB):

The Transparency Commission considers that PROLIA contributes minor (IV) improvement in actual benefit as second-line therapy after bisphosphonates in the management of postmenopausal osteoporosis.

4.3. Therapeutic use

Current strategy:
Osteoporosis is defined by a T-score ≤ -2.5 in the absence of any other cause of a demineralising bone disease or bone fragility. The purpose of treatment of osteoporosis is to prevent fractures.
Calcium and vitamin D should be tested and any deficiency corrected before any antiosteoporosis agents are started. Vitamin and calcium supplementation should be continued if necessary during antiosteoporosis therapy.

According to the AFSSAPS guidelines published in January 2006, osteoporosis complicated by fracture should routinely be treated. In postmenopausal women with no previous fracture, the indication for treatment should be discussed for each individual case, according to the individual fracture risk. This risk is assessed from the T-score value and the presence if any of other risk factors for fractures. Treatment should therefore be considered in women with:

- a substantial decrease in bone mineral density (T score < - 3) or
- T score ≤ -2.5 combined with other risk factors for fracture, particularly age > 60 years, previous or current systemic corticosteroid therapy at a dosage of ≥ 7.5 mg/day prednisone equivalent, body mass index < 19 kg/m², previous fracture of the femoral neck in a first-degree relative (mother), early menopause (before the age of 40).

In the absence of any direct comparison between the various antiosteoporosis agents (bisphosphonates, raloxifene, teriparatide and strontium ranelate), treatment should be chosen according to the risk of vertebral and/or nonvertebral fracture, age, the number and site of fractures, and the patient's background and current situation and any contraindications to any of the medicinal products.

Only certain bisphosphonates and strontium ranelate simultaneously reduce the risk of vertebral and hip fractures.

If a fracture occurs after the first year of treatment despite satisfactory compliance, treatment should be reconsidered. Another medicinal product may be proposed, including one from the same pharmacological category.

Place of PROLIA (denosumab) in the treatment strategy
The proprietary medicinal product PROLIA (denosumab) is the first biological agent with an indication for treatment of postmenopausal osteoporosis. It is administered by subcutaneous injection once every six months. Its efficacy has been demonstrated in terms of reducing the risk of vertebral and nonvertebral fracture including femoral neck fracture. According to the available data, there is three years' experience of treatment with PROLIA with evidence of an anti-fracture effect compared with placebo, and the maximum follow-up of treated patients is five years. There is little experience in terms of tolerance,

In a female patient with increased fracture risk who cannot continue bisphosphonate therapy, PROLIA is a useful alternative to strontium ranelate and to teriparatide (efficacy not demonstrated for femoral neck fracture).

4.4. Target population

The target population for PROLIA is women with postmenopausal osteoporosis who are at increased risk of fracture and receiving bisphosphonate therapy which cannot be continued.

The population of postmenopausal women with osteoporosis can be estimated from the following data:

- approximately 25-40% of women aged 65 years and 50-70% of women aged 80 years have osteoporosis[i,ii]
- applied to the female population updated on 1 January 2010, and taking account of a linear progression of prevalence between 65 years and 80 years.

These data allow us to estimate the population with postmenopausal osteoporosis as between 2.5 and 3.6 million women.

Only part of this population is eligible for treatment with PROLIA but in the absence of precise epidemiological data, it is difficult to estimate this population.

4.5. Transparency Committee recommendations

The transparency Committee recommends only in the indication "treatment of osteoporosis in women at increased risk of fractures, after bisphosphonate therapy" on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services.

4.5.1. Reimbursement limits

Treatment of postmenopausal osteoporosis in patients at high risk of fracture as second-line therapy after bisphosphonates.

Patients at high risk of fracture are defined as:

- patients who have had a fracture caused by bone fragility,
- in the absence of fracture, women with a substantial decrease in bone density (T score < -3) or with a T score ≤ -2.5 combined with other risk factors for fracture, particularly age > 60 years, previous or current systemic corticosteroid therapy at a dosage of ≥ 7.5 mg/day prednisone equivalent, body mass index < 19 kg/m², previous fracture of the femoral neck in a first-degree relative (mother), early menopause (before the age of 40).

4.5.2. Packaging: Appropriate for the prescription conditions

4.5.3. Reimbursement rate: 65%

4.5.4. Request for a post-listing study:

The Transparency Committee
In view of the fact that:

- the efficacy of PROLIA compared with the alternative therapies currently available in France cannot be completely established from indirect comparisons derived from a meta-analysis with mixed effects due to the demonstration of both inconsistencies and a modest gain in efficacy by PROLIA compared with the available alternatives;
- no studies were submitted that directly compared the anti-fracture effect of PROLIA with that of an antiosteoporosis agent (including an oral bisphosphonate which has been available for a long time);
- the benefit of replacing bisphosphonates with PROLIA is only based on an intermediate endpoint;
- PROLIA is the first monoclonal antibody acting on the RANK ligand (RANKL) that has had an indication in osteoporosis approved;
- long-term tolerance is unknown;
- better patient compliance related to the administration method of one SC injection every six months has not been demonstrated;
- there are doubts about the role that PROLIA will play in the treatment strategy in practice

The applicant is asked to provide data from a representative population of treated women with osteoporosis (irrespective of treatment) on the role of PROLIA in the treatment strategy and to provide details of its efficacy against fractures, compliance and long-term tolerance in real life. The methods will be specified later.

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[i] *Société Française de rhumatologie* [French Rheumatology Society]. Osteoporosis dossier 2005. Why is osteoporosis called a public health problem? (http://www.rhumatologie.asso.fr/04-Rhumatismes/grandes-maladies/0A-dossier-osteoporose/sommaire-osteoporose.asp)

[ii] Ministry of Health, the Family and People with Disabilities. *Direction générale de la Santé* (Ministry of Health). Report by GTNDO (the French expert group that establishes public health objectives). Analysis of available knowledge about selected health problems, their influencing factors, and public health strategies: Definition of objectives. March 2006. (http://www.ladocumentationfrancaise.fr/rapports-publics/034000115/index.shtml